

Exhibit C

LEWIS'S CHILD AND ADOLESCENT PSYCHIATRY

A Comprehensive Textbook

Andrés Martin
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FIFTH EDITION



Wolters Kluwer

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5th edition

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9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data

Names: Martin, Andrés, editor. | Volkmar, Fred R., editor. | Bloch, Michael (Michael Howard), editor.

Title: Lewis's child and adolescent psychiatry : a comprehensive textbook / editors, Andrés Martin, Fred R. Volkmar, Michael Bloch.

Other titles: Child and adolescent psychiatry

Description: Fifth edition. | Philadelphia : Wolters Kluwer, [2018] | Includes bibliographical references.

Identifiers: LCCN 2017025399 | ISBN 9781496396587

Subjects: | MESH: Mental Disorders | Infant | Child | Adolescent

Classification: LCC RJ131 | NLM WS 350 | DDC 618.92/89—dc23

LC record available at <https://lccn.loc.gov/2017025399>

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CHAPTER 5.14 ■ GENDER DYSPHORIA AND GENDER INCONGRUENCE

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INTRODUCTION

Transgender (gender incongruent) youth include children and adolescents who experience a marked incongruence between their gender assigned at birth and their gender identity (1). Since the last edition of this volume, which was published 10 years ago (2), there has been a remarkable increase in attention to transgender issues across the life span. Television has begun to highlight transgender individuals from childhood to adulthood (3,4). News outlets from *The New York Times Magazine* to *Le Monde* have explored the life experiences of transgender youth (5–7). Legislative bodies have examined transgender rights through restroom access, hate crime legislation, insurance regulations, and antidiscrimination policies, with physicians playing key roles in these discussions (8). Parallel to this growing attention, there has been a marked increase in the establishment of specialized gender identity clinics for children and adolescents in North America and in Europe (9), which likely reflects the marked increase in referrals that has been noted internationally (10–12). At the same time, the scientific literature on gender incongruence has expanded as well, with a flux of new studies on co-occurring psychological functioning, long-term follow-up studies, biologic correlates, and outcomes of medical interventions. Practicing child and adolescent psychiatrists should be familiar with the basics of this field to appropriately assess and treat these patients.

TABLE 5.14.1

TERMINOLOGY

Term	Definition
Gender assigned at birth/natal sex/birth sex	Gender assigned to an infant at birth, generally based on physical characteristics (genitalia, etc.)
Experienced gender/gender identity	An individual's psychological understanding of one's own gender
Affirmed gender	An individual's psychological understanding of one's own gender, typically referring to one who lives socially as that understood gender
Sexuality/sexual orientation	Refers to the types of individuals toward whom one is romantically and/or sexually attracted
Transgender	Refers to an individual whose gender identity is incongruent with that of one's gender assigned at birth. Sometimes also used as a term for an individual whose gender identity is binary opposite one's gender assigned at birth.
Gender dysphoria	Refers to psychological distress in relationship to one's experienced gender; is also the classification used in the DSM 5 (requiring fulfillment of certain

	clinical criteria)
Cisgender	Refers to an individual whose experienced gender matches that of one's gender assigned at birth
Gender non-conforming/gender variant	Refers to variation from developmental norms in gender role behavior that may be considered as nongender stereotypical. This may include identifying as both genders or identifying with neither gender, among others.
Transsexual	Typically used to refer to individuals who desire medical interventions to align their physiologies with the gender identities. This term is used synonymously with transgender by some and has largely fallen out of favor (though it was used commonly in the past).

TERMINOLOGY AND DEFINITIONS

Terminology in this specialized area is continuously evolving. This section describes terms and definitions that are in most common usage at this time, but different regions, cultures, and families may have their own preferred terminology ([Table 5.14.1](#)).

The term *gender assigned at birth* refers to a newborn's gender (boy, girl, indeterminate), as generally declared by a medical professional. Other relevant terms include *natal sex* and *birth sex*. The term *biologic sex* is somewhat vague, as it is unclear whether it would be based on karyotyping of the sex chromosomes, internal reproductive structures, the configuration of the external genitalia, etc. The vast majority of newborns are assigned the gender of boy or girl through prenatal diagnostics or, at birth, based on genital anatomy. A small number of newborns may be classified as having a "disorder of sex development" (DSD), or what others have called "differences of sex development" ([13](#)), congenital conditions in which biologic parameters of sex (e.g., the sex chromosomes, the gonads or the configuration of the external genitalia, etc.) are incongruent with one another. These conditions include complete or partial androgen insensitivity syndrome, mixed gonadal dysgenesis, 5-alpha-reductase deficiency, penile agenesis, and congenital adrenal hyperplasia (CAH), among others. Such patients may experience gender identity issues that can be unique from those experienced by those without a DSD ([14](#)).

Experienced gender refers to one's gendered sense of self as a boy, as a girl, or some alternative gender that is different from the traditional boy–girl dichotomy (e.g., "gender fluid," "agender," or "nonbinary"). Other terms include *affirmed gender* (typically used for individuals who have transitioned socially to living as the desired gender). For the majority of individuals, experienced gender matches the gender assigned at birth. These individuals are referred to as *cisgender*. For some patients, experienced gender is opposite from the gender assigned at birth, and these individuals are referred to as *transgender*.

Transgender, *gender variant*, and *gender nonconforming* are sometimes used as terms for individuals whose experienced gender does not strictly match that of their

gender assigned at birth. One who experiences psychological distress in relation to one's gender identity may be referred to as *gender dysphoric*. Gender dysphoria is the diagnostic term that has been adopted in the DSM-5 (see below) (1).

Sexual attraction or *sexual orientation* is a separate concept from gender identity. Sexual orientation refers to the types of individuals toward whom one is romantically or sexually attracted. Terms such as androphilia (attraction to males), gynephilia (attraction to females), biphilia (attraction to males and females), and aphilia (attraction to neither males nor females) are used more commonly nowadays, slowly replacing older terms such as heterosexual, bisexual, homosexual, and asexual. In the scientific literature, the sexual orientation of individuals who identify as transgender can be described in relation to their experienced gender or their gender assigned at birth. For example, an adolescent female who identifies as male and is sexually attracted to females can be described as "heterosexual" in relation to experienced gender but as "homosexual" in relation to birth sex (15). From either a clinical or research perspective, it is critical to identify the referent in describing a patient's sexual orientation. Most individuals who identify as transgender will describe their sexual orientation in relation to their gender identity, not their gender assigned at birth (e.g., a transgender woman who is attracted to men would likely consider herself to be heterosexual).

The "genderbread person" has been developed as an educational tool to clarify the distinctions among *gender assigned at birth*, *experienced gender*, and *sexual orientation* (Figure 5.14.1). Note that as a published educational instrument, this graphic diverges somewhat from the contemporary terminology we described above. Nonetheless, this tool has proven useful for introducing this terminology to families and students new to the topics of gender and sexuality.

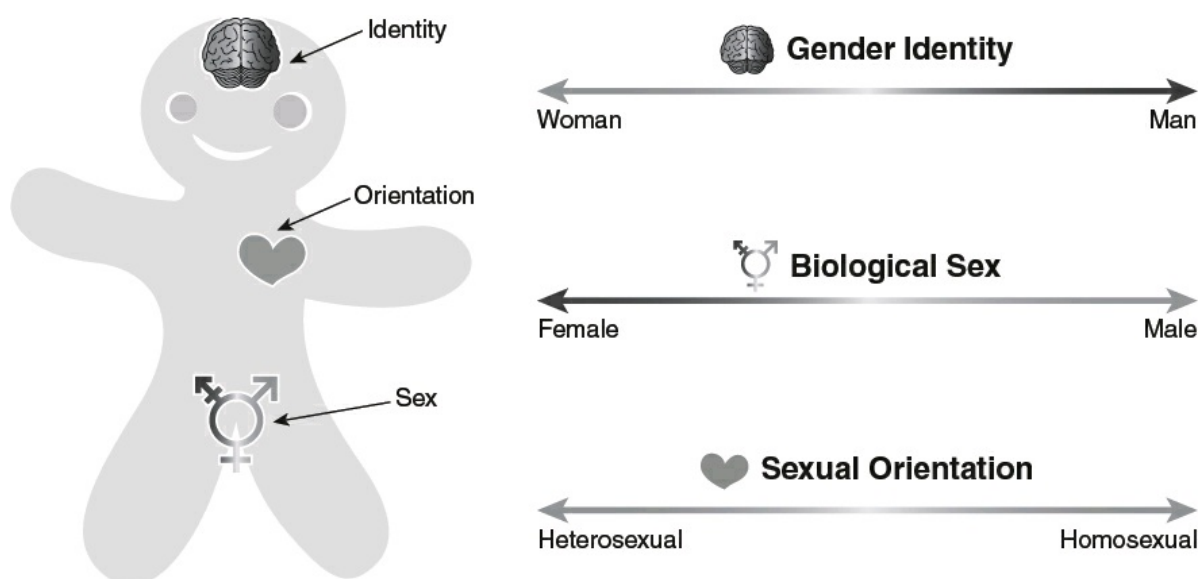


FIGURE 5.14.1. The Genderbread Person. The genderbread person is an educational tool used to explain the distinctions between experienced gender (termed gender identity here), gender

assigned at birth (termed biological sex here), and sexual or romantic orientation. This educational tool may be useful for students new to the field and when explaining these phenomena to families with gender incongruent and gender dysphoric children. These terms are further described in [Table 5.14.1](#). (Modified from Killermann S. (2016). *The Genderbread Person*. Available at: itspronouncedmetrosexual.com)

HISTORY OF GENDER IDENTITY AND MEDICINE

John Money (1921–2006) was a psychologist and sexologist whose empirical and theoretical contributions regarding gender identity, gender role, and gender development were innovative and of great influence, beginning in the 1950s. Money originally proposed a theory of “gender neutrality,” suggesting that gender identity was predominantly determined by social factors, including the gender assigned at birth and subsequent socialization processes (16). Money proposed that, for individuals with a DSD, early surgical interventions to correct genital ambiguity were often needed so that a child could then be supported with rearing in the gender assigned at birth.

Over the past few decades, Money’s original theory of gender neutrality at birth has been challenged by various lines of evidence suggesting the importance of biologic factors, particularly patterns of prenatal hormone exposure, in also contributing to gender identity formation and differentiation. For example, chromosomal females with CAH, assigned female at birth are exposed to elevated levels of prenatal testosterone and many of these girls are behaviorally masculinized and a higher percentage than the general population develop gender dysphoria and transition from male to female (17,18).

Perhaps the most widely cited case pertains to a biologically “normal” male (one of a pair of identical twins) who, after a circumcision accident at the age of 7 months led to penile ablation, underwent a vaginoplasty and was socially reassigned to female at the age of 17 months (19,20).

Although this patient was described by Money (21) as a “tomboy” during childhood, subsequent follow-up revealed that the patient rejected estrogen therapy at the time of puberty and subsequently transitioned back to living as a male (19,20). Tragically, this patient committed suicide at the age of 38 (22). The “John–Joan” case, as it was called, has been used as evidence of the importance of biologic factors in contributing to a person’s sense of gender identity. A subsequent summary of seven similar such patients reared as female after traumatic loss of the penis have shown both male and female gender identities in adolescence and adulthood, further complicating the picture (23).

In the 1960s, research into the developmental histories of adults with

“transsexualism” suggested that childhood cross-gender identification was common in these individuals (24). This work was then followed by research with children who showed patterns of gender-related behavior similar to the recalled patterns of transsexual adults (24). During this period, there was much less attention given to adolescents with a marked history of cross-gender identification.

By the late 1990s, however, more attention was given to adolescents with a DSM diagnosis of gender identity disorder, including the possibility of treatments with gonadotropin-releasing hormone analogs (GnRHa), as reported by a research team in the Netherlands (25). This approach, described below, was ultimately outlined in the 2009 Endocrine Society Guidelines for the Treatment of Transsexual Persons (26) and in the periodically updated Standards of Care by the World Professional Association for Transgender Health (27). Research into these hormonal interventions has since garnered significant attention, including increased NIH funding to study the long-term benefits and risks of these endocrine treatments (28).

DIAGNOSIS AND ASSESSMENT

Gender identity diagnoses first entered the DSM in its third edition with three diagnoses: transsexualism, gender identity disorder of childhood, and atypical gender identity disorder. The essential feature of these three diagnoses was “an incongruence between anatomic sex and gender identity” (29). Revisions in the DSM-III-R were modest, though in this edition, exclusion of individuals with schizophrenia or a DSD was removed, noting that individuals with either of these diagnoses could also have a gender identity disorder (30).

In the DSM-IV, the three diagnoses from DSM-III were collapsed into the overarching diagnosis “gender identity disorder” with distinct criteria sets for children versus adolescents and adults. This edition also added a criterion stating “The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning” (31).

The DSM-5 renamed “gender identity disorder” as “gender dysphoria,” aiming to decrease stigma associated with the diagnosis while maintaining a diagnosis that could be used to secure access to care for those who needed it (32). The DSM-5 removed sexual orientation subtyping, but noted in the text its relevance in understanding variations in developmental trajectories and for research on biologic factors and long-term outcomes (1). The DSM-5 also made an effort to make the childhood diagnosis stricter, requiring more than just gender nonconforming behavior. The new criteria required that a child expresses an actual desire or insistence of being the other gender. The adolescent and adult criteria simultaneously became more inclusive, allowing for nonbinary gender identities that would allow for gender variant, but not strictly binary, transgender adolescents and adults to receive the diagnosis and subsequently access to care.

Current DSM-5 criteria for gender dysphoria in children require a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as evidenced by at least six of eight criteria, one of which must be a strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender) (1). Additionally, the patient must experience clinically significant distress or impairment in social, school, or other important areas of functioning as introduced in the DSM-IV (Table 5.14.2). DSM-5 criteria for gender dysphoria in adolescents and adults are similar, though with different requirements for the manifestation of gender dysphoria. This diagnosis requires at least two of six manifestations (Table 5.14.3). For a summary and rationale for the DSM-5 changes, see Zucker et al. (33).

Some have argued for use of the term "gender incongruence," including the Working Group on Sexual Disorders and Sexual Health for the forthcoming 11th edition of the International Classification of Diseases. This group suggested that the term gender incongruence highlights that not all transgender individuals experience dysphoria. The group noted that the term gender dysphoria might increase inappropriate stigmatization and pathologization. Only for the practical purpose of preserving access to medical care did the group recognize the necessity of classification. The group additionally argued that the diagnosis be moved out of the chapter on mental health and behavioral disorders and into another section, provisionally termed Conditions Related to Sexual Health (34).

TABLE 5.14.2

DSM-5 CRITERIA FOR GENDER DYSPHORIA IN CHILDREN AND IN ADOLESCENTS AND ADULTS

Diagnostic Criteria

Gender Dysphoria in Children

302.6 (F64.2)

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):
 - 1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
 - 2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
 - 3. A strong preference for cross-gender roles in make-believe play or fantasy play.
 - 4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
 - 5. A strong preference for playmates of the other gender.
 - 6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
 - 7. A strong dislike of one's sexual anatomy.
 - 8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.
- B. The condition is associated with clinically significant distress or impairment in social, school, or

other important areas of functioning.

Specify if:

- With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).
- **Coding note:** Code the disorder of sex development as well as gender dysphoria.

Gender Dysphoria in Adolescents and Adults

302.85 (F64.1)

- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
 2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
 3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
 4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
 5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).
- B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

- **With a disorder of sex development** (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).
- **Coding note:** Code the disorder of sex development as well as gender dysphoria.

Specify if:

- **Posttransition:** The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

TABLE 5.14.3

TREATMENT OF TRANSGENDER YOUTH

Timing	Intervention
Prepubertal	No endocrine intervention recommended. Patient should have regular psychotherapy to discuss gender identity and assess possible future need for hormonal intervention.
Early signs of puberty	Pubertal blockade with gonadotropin-releasing hormone analogs to prevent the development of secondary sex characteristics and provide additional time for psychotherapy and consideration regarding partially reversible interventions.
Age 14+ or 16+, depending on the center	Cross-sex hormonal therapy with estrogen or testosterone. Less frequently with other endocrine-acting medications that have less favorable side effect profiles.
Age 18 for most centers	Gender-affirming surgeries may be considered. Note that some surgeries may be performed earlier for select patients (generally mastectomies for transgender males).

EPIDEMIOLOGY OF GENDER DYSPHORIA AND GENDER NONCONFORMITY

A range of methodologic challenges, including but not limited to shifting terminology and stigma associated with self-identification, have made it difficult to establish the true prevalence of gender dysphoria or gender incongruence.

Prevalence in Adults

In adults, most studies have used the numbers of individuals that seek out clinical care for gender-affirming treatment as a proxy for determining prevalence in a certain country or catchment area. A recent meta-analysis based on 21 studies that applied this method concluded that the prevalence of transsexualism (the definition used in most of these studies) was 6.8 transwomen in 100,000 gender at birth-assigned males (1:14,705) and 2.6 transmen in 100,000 gender at birth-assigned females (1:38,461) (35). A time trend was also found, with recent studies reporting higher prevalence rates. These studies are, of course, limited by the fact that they do not include transgender individuals who do not seek medical care. Indeed, much higher prevalence rates, ranging from 4.2% having an ambivalent gender identity to around 0.5% identifying as transgender and considering medical interventions, are suggested by recent studies that have used broader definitions and probability samples (36–38). A recent population-based survey in the United States found that 0.6% of adults self-identified as transgender, with rates ranging from 0.3% to 0.8% in the states for which data were available. Compared to the older age groups, young adults between 18 and 24 years old were most likely to identify as transgender (39).

Prevalence in Children and Adolescents

Although formal epidemiologic studies of gender dysphoria in children and adolescents have not been conducted, looser or more liberal definitions of “caseness” in children and adolescents have been examined in several recent studies. In a random sample of 2,730 grade 6 to 8 students from San Francisco, Shields et al. (40) found that 1.3% self-identified as “transgender” in response to the question “What is your gender?” with the other response options being female or male. In a random sample of 8,166 high school students from New Zealand, Clark et al. (41) found that 1.2% self-identified as transgender and 2.5% reported that they were not sure about their gender, in response to the question “Do you think you are a transgender?” which was followed by a definition of the term. Interestingly, another 1.7% reported that they did not understand the question.

In the 1999 standardization sample of the Child Behavior Checklist (CBCL) for children aged 6 to 18 years and the Youth Self-Report (YSR) form, aged 11 to 18

years, there is one item pertaining to gender identity (“Wishes to be of opposite sex”) (42). On the CBCL (total $N = 3,210$), less than 1% of parents of nonreferred boys and 1.2% of nonreferred girls endorsed this item as either somewhat or sometimes true or very true or often true. The percentages were higher for referred boys and girls (2.8% and 5.4%, respectively). On the YSR, about 10% of nonreferred girls and 2% of nonreferred boys endorsed this item compared to about 18% of referred girls and 3% of referred boys. In the prior 1991 CBCL standardization sample, two age groups were reported (4 to 11 and 12 to 18). For the 4 to 11 year olds, 1% of parents of nonreferred boys and girls endorsed this item compared to 3% and 5% of referred boys and girls. For the 12 to 18 year olds, none of the parents endorsed this item for nonreferred boys and girls compared to 2% and 5% of referred boys and girls. Consistent with the original CBCL and YSR standardization studies, two consistent findings emerge: the item is endorsed more often for girls than for boys and it is endorsed more often for referred than for nonreferred children and adolescents.

Gender Assigned at Birth Ratio

Of prepubertal children referred to gender identity clinics, the majority has a male gender assigned at birth. Among 577 Canadian children referred to a gender identity clinic between 1976 and 2011, the male-to-female ratio was 4.49:1 (12). This was significantly higher than the 2.02:1 ratio in the Netherlands (12). These differences are theorized, in part, to be a reflection of increased parental anxiety regarding gender-variant behavior in males compared to females, particularly in North America. For adolescents with gender dysphoria, the gender ratio is much closer to 1:1 and appears to be more consistent across nations (10). Of note, however, there has been a recent temporal shift from more birth-assigned males (prior to 2006) to more birth-assigned females (2006 to 2013), though the ratio remains closer to 2:1 in either direction (10).

BIOLOGIC AND PSYCHOSOCIAL DETERMINANTS

The etiology of cross-gender identification and behavior continues to be elusive. While psychological and social factors were once the focus of study, especially in normative gender development, attention has shifted to biologic mechanisms more recently. At present, the evidence suggests that both psychosocial and biologic elements are involved. A monocausal mechanism is unlikely and gender dysphoria most likely results from a complex interaction between these factors (43).

Biologic Factors

Twin studies suggest a strong heritable component with additional environmental

contributors. In a large-scale CBCL study of Dutch twins ($N = 23,393$) ages 7 and 10 (44), monozygotic (MZ) and dizygotic (DZ) twins were compared and estimated genetic factors contributed to 70% of cross-gender behavior (as assessed via the two CBCL gender items). Another study of 314 MZ and DZ twins (mean ages 9.4 and 10.1 years, respectively) roughly replicated this finding, with genetic factors contributing to 62% of the variance on a DSM-IV-based gender dysphoria scale (45). In a third study of 3,337 Japanese MZ and DZ twins ranging in age from 3 to 26 years (46), there was also strong evidence for genetic factors for females, but much less so for males.

Many studies, both in animals and humans, have shown that differences in brain anatomy and function in cis-gender males and females underlie the sex differences in their behavioral (47). Sex hormones play an important role in these differences. The *organizational* effect, predominantly prenatally but also during puberty, leads to the sex differences in brain structures. On average, males have larger brain volumes, more white matter, gray matter, and cerebrospinal fluid than females, although when corrected for total volume, females have more gray matter and a larger volume of the cortex (48–50).

The sexual differentiation hypothesis suggests that transgender individuals may have brain structures and brain functioning more closely aligned with their experienced gender (51). Postmortem studies have suggested a sex reversal in several hypothalamic nuclei in transgender adults (52,53). More recent neuroimaging techniques have allowed the *in vivo* study of brain morphology and functioning of larger numbers of adolescents and adults with gender incongruent feelings (50,54). Findings of these studies are more mixed. Before they received any medical gender affirmative treatment, brain anatomy with regard to volume, gray and white matter, and cerebrospinal fluid did not differ compared to their birth-assigned sex (50). Differences are, however, found with regard to the white matter microstructure, with results of transgender individuals in between males and females (50). In the realm of functional neuroimaging, task-related imaging studies show that transgender people may have either similar reactions as their experienced gender (e.g., smelling odorous steroids (55)) or activity different from their assigned gender as well as their experienced gender (e.g., mental rotation (56)), or not different from their assigned gender (e.g., verbal fluency (57)). The results so far show that we are still far away from a situation where imaging or other medical testing may serve as a diagnostic tool.

In animal studies, where prenatal hormones can be manipulated, the strong effect of prenatal testosterone on gender role behavior is clear (47). The effects on gender identity, however, can only be studied in humans. Individuals with DSD may be exposed to high levels of prenatal testosterone, and XX individuals with CAH (58) indeed have higher rates of gender dysphoria and cross-gender identification (18). The majority of female-raised individuals with CAH (~95%), however, appear to

develop a female gender identity (17). Other evidence for the importance of prenatal testosterone comes from studies in XY individuals with complete androgen insensitivity syndrome (CAIS) who lack the receptors necessary to respond to endogenous testosterone. The vast majority of these patients develop a female gender identity, suggesting that downstream testosterone signaling may be important for the development of a male gender identity (59). Others have noted that these patients are reared unambiguously as females and that social factors may play a strong role in their female identity formation (60). Some studies have shown that those with CAIS have lower scores on tests of female identity scales (61) and there have been some case reports of gender dysphoria ultimately leading to gender-affirming surgeries (62). This notably could be secondary to the psychological stress of learning about the diagnosis, as well as the possibility of undetected functional androgen receptors (43). Overall, studies of gender identity in individuals with DSD, while implicating androgens in the development of gender identity, have yet to show a simple direct relationship.

Psychosocial Factors

Past literature has investigated the potential role of parental characteristics on the development of gender dysphoria (maternal wish for a child of the opposite gender, paternal absence, and parental psychological functioning, among others). None of these hypotheses have been validated (43). Mothers of gender dysphoric boys have been noted to have higher scores on the Beck Depression Inventory and the Diagnostic Interview for Borderlines (63), but these higher scores might be due to external pressures placed on these parents by unaccepting social environments and such studies cannot determine the direction of causation. One study noted that gender dysphoric boys were rated as more feminine and “beautiful” by blinded college students (64) while another study of gender dysphoric girls showed that these girls were rated as less “cute” (65), raising the question of whether perceived physical appearance and resultant social treatment may contribute to gender incongruence. An alternative interpretation of this data is that those with a more male gender identity might alter their appearances to appear more “masculine” (e.g., culturally masculine haircuts) while those with a more female gender identity alter their appearances to appear more “feminine” (66). Some have suggested that a lack of parental limit-setting, particularly around cross-gender behavior, is associated with gender dysphoria (67), though this again does not prove causation, as more insistence on cross-gender behavior (i.e., transgender identity or stronger cross-gender behavior preferences) may make this limit-setting more difficult. Overall, there have been no proven causative psychosocial factors in the development of gender incongruence. Since studies on normative gender identity development show that cognitive psychological factors and social environment play a role, this may also be the case

for gender nonconforming development.

CLINICAL COURSE

Persistence of Gender Dysphoria from Childhood to Adolescence

The natural history of gender identity for children who express gender nonconforming or transgender identities is an area of active research (68). To date, the long-term follow-up studies of clinic-referred children have been based on samples that have included children who were either threshold or subthreshold for the gender identity diagnosis in DSM-III, III-R, or IV and some of the earliest studies began prior to the availability of formal diagnostic criteria.

These follow-up studies have classified participants as either “persisters” or “desisters” with regard to their cross-gender identification, using various metrics (semi-structured interviews based on DSM criteria for gender identity disorder, dimensional scores on standardized questionnaires, etc.). Ristori and Steensma (69) have provided the most recent summary of 10 follow-up studies, in which the percentage of participants classified as persisters ranged from 2% to 39% (collapsed across natal boys and girls). In one study (70), the percentage of natal girls who were persisters appeared to be substantially higher than the percentage of natal boys (50% vs. 12%), but in two other studies from the same clinic, the percentage was similar across natal sex (71,72).

One criticism of these studies is that either formal diagnostic criteria were not used (because they were not available at the time of the study) or that subthreshold cases were included. Some studies have found that threshold cases were more likely to be classified as persisters (73), but other studies have not (72). It has also been suggested that more recent cohorts (after the year 2000) have found higher rates of persistence (12% to 39% (61,64–66)) than older cohorts (2% to 9% prior to 2000 (74,75)); however, it is not clear if such differences are related to variations in sampling procedures or something more substantive. Comparisons of persisters with desisters have found that the intensity of gender dysphoria (using dimensional metrics), older age at the time of assessment in childhood, a lower social class background, and having a female gender assigned at birth are associated with higher rates of persistence (72,73). Despite this work, it remains difficult to predict, for an individual child, the likelihood of cross-gender identification persistence from childhood into adolescence (73).

Persistence of Gender Dysphoria from Adolescence to Adulthood

In contrast to the low rates of persistence from childhood into adolescence, it appears that the vast majority of transgender adolescents persist in their transgender identity (76).

Childhood Gender-Variant Behavior and Sexual Orientation

Childhood gender-variant behavior has been found to be a strong predictor of a same-sex sexual orientation (using gender assigned at birth as a reference point) in adults. In a study of 879 Dutch boys and girls, gender-variant behavior was assessed using the CBCL and sexual orientation was assessed 24 years later (77). It was found that the prevalence of a same-sex sexual orientation was, depending on the domain (attraction, fantasy, behavior, and identity), between 8.4 and 15.8 times higher in the gender-variant subgroup as compared to the nongender-variant subgroup. In summary, the current literature, though limited as described above, suggests that the majority of gender incongruent prepubescent children will grow up to identify as cisgender individuals with either a bisexual or a same-sex sexual orientation (70,72,74).

ASSOCIATED COEXISTING PSYCHIATRIC CONDITIONS AND BEHAVIORS

Children and adolescents with gender incongruence exhibit higher internalizing and externalizing psychopathology as compared to nonreferred controls, with internalizing psychopathology being more common, particularly in natal boys (78–84). One hypothesis is that this problem behavior is a result of minority stress and dysphoria toward their gender assigned at birth. These individuals are also subjected to rates of peer bullying as high as 80% (85). Poor peer relations is one of the strongest investigated predictors for behavioral and emotional problems in gender incongruent youth (79). In a study of 105 gender dysphoric Dutch adolescents whose parents completed the Diagnostic Interview Schedule for Children (DISC), 32.4% had one or more psychiatric disorders, with 21% suffering from anxiety, 12.4% from mood disorders, and 11.4% from disruptive disorders (85). A study with the same DISC measure in prepubertal children revealed higher percentages, with 52% having one or more psychiatric disorders other than GD (80).

Chart review studies of gender incongruent youth presenting to specialized gender identity clinics have shown similarly high or even higher rates of psychiatric conditions: mood (12.4% to 64%), anxiety (16.3% to 55%), and disruptive disorders (9% to 11.4%) (82,83,86–88). The prevalence range across studies may be secondary to cultural differences, differing diagnostic criteria, and differing ages of clinical populations. These psychiatric conditions appear to become more common in

gender incongruent individuals with increasing age. Some studies have shown that older transgender youth suffer a greater burden of co-occurring psychiatric conditions (82), and that gender incongruent adults suffer a greater burden of co-occurring psychiatric conditions as compared to adolescents (89).

Self-harming Behavior and Suicidality

Self-harming behavior and suicide attempts are prevalent among gender incongruent youth. Gender clinics have reported high rates of past suicide attempts by patients presenting for care: Boston (9.3%, mean age 14.8 (87)), London (10%, mean age 13.5 (82)), Los Angeles (30%, mean age 19.2 (86)). Rates of self-harm and suicidality appear to increase with age within this population (90).

Autism Spectrum Disorder

A number of studies have shown autism spectrum disorder (ASD) symptoms to be over-represented among transgender individuals. Clinical level rates of ASD symptomatology in transgender adults have been reported in the range of approximately 5% to 20% (91–93). A single study of 204 children and adolescents referred for gender dysphoria reported an ASD prevalence of 7.8% as measured by the Diagnostic Interview for Social and Communication Disorders (94). This compares to rates of ASD in the general population of around 1% (95). Two studies found increased gender variance (5.4%, 11.3%), defined by a positive response to “wishes to be of opposite sex” sometimes or often on the CBCL or YSR) in referred children, adolescents, and adults with ASD compared to nonreferred controls (96,97). However, the same was true for an ADHD-referred control sample (97), raising the issue that a higher probability of gender variance is characteristic of clinic-referred samples in general. Several hypotheses for shared underlying etiology that explains the link between these two conditions have been suggested (98–100).

Clinically, the co-occurrence of gender dysphoria and ASD may complicate transgender care, as diagnosing gender dysphoria can be difficult (e.g., in the context of the rigid thinking that is characteristic of ASD). Case reports have described instances cross-gender identification represented a transient preoccupation in youth with ASD (101). Additionally, language difficulties can make expression of gender dysphoria difficult for patients with ASD. Nonetheless, a comprehensive narrative review of the literature has shown a role for transition with pubertal blockade and cross-sex hormonal therapy in these patients following an extended diagnostic process (99). By use of a Delphi method, a group of experts on the ASD-gender dysphoria co-occurrence developed initial clinical guidelines assessment and treatment for adolescent transgender care (98). Careful diagnosis of both conditions by specific specialists, collaboration of clinicians from both fields, an extended

diagnostic phase, and risk assessment and safety issues are part of the suggested management protocol.

THERAPEUTICS

Treatment of Prepubescent Children

Over the past 10 years, best practice treatment for children with gender dysphoria has been the subject of intense controversy (102). As noted below, there are now three broad approaches that have been delineated in the literature: (1) the oldest one—characterized by Dreger (103) as the “therapeutic model”—consists of efforts, either directly (e.g., via specific suggestions that parents can implement in the day-to-day environment) or indirectly (e.g., psychodynamically informed approaches that treat the putative underlying “causes” of the gender dysphoria) and actively attempt to reduce cross-gender identification (104); (2) an intermediate approach, which some have characterized as “watchful waiting” (105), in which no direct efforts are made to “prohibit” a child’s gender-variant behavior, but one that also advises parents to keep options open about the child’s long-term gender identity and to avoid early social transition; (3) and, more recently, an approach characterized by Ehrensaft (106) as the “affirmative model” that considers all outcomes of gender identity to be equally valid and desirable and allows children who express a desire to socially transition to do so after careful counseling. These approaches have been discussed in great detail in three Task Force reports (107–109), in a special volume of the *Journal of Homosexuality* (102), and various other essays and case reports, the references for which can be found in these major reviews.

For the nonspecialist, there are several key issues to keep in mind when appraising this literature: (1) Some of these approaches may be influenced by particular theoretical formulations regarding the determinants of gender dysphoria and these formulations guide or influence recommended treatment plans; (2) there are no randomized controlled trials that have compared the effects of these treatments with regard to both short-term and long-term outcomes. Indeed, Byne et al. (109) noted that, by and large, “the highest level of evidence ... can best be characterized as expert opinion” (p. 762); (3) with some rare exceptions (110), there are no manualized or even semi-manualized treatments that a clinician can follow in developing a therapeutic plan. Thus, the clinician needs to self-educate by reading about the therapeutic model that one intends to follow and tailor it on a case-by-case basis. Below, we provide relatively brief summaries of these three treatment approaches.

Promoting Identification with the Gender Assigned at Birth

This first approach aims, through psychosocial interventions, to reduce the child's cross-gender identification and gender dysphoria. These treatments (which have been described in the literature since the 1960s) have, however, been quite varied. They include classical behavior therapy, psychodynamic therapy (including psychoanalysis and dynamically informed play psychotherapy), parental counseling, and parent-guided interventions in the naturalistic environment (e.g., encouragement of peer relations of the same natal sex) (110,111).

Perhaps the underlying assumption of all of these approaches rests on the view that gender identity is not yet fixed in childhood and may be malleable through psychosocial treatments. There is also an implicit assumption or value judgment that might be inferred from this approach, namely that all things considered a child's long-term adaptation might be easier if he or she could come to feel content with a gender identity that matches their natal sex and to avoid the necessity of a lifelong regimen of cross-sex hormonal treatment and sex-reassignment surgery (or what nowadays is also called gender-affirming surgery).

Critics of this approach have argued that there is nothing inherently "wrong" with a cross-gender identity and have challenged the view that trying to change such an identity is warranted. Indeed, there are now several US states and one province in Canada that have passed legislation stating that it is inappropriate to try and change a minor's gender identity when the minor is unable to consent to the treatment, but exempt from this directive is "identity exploration" (112). Critics have also rightly noted that some of the earliest proponents of this treatment held the belief that it might also reduce the odds of the child's later development of a same-sex sexual orientation (113), although other proponents of this treatment rejected this as an ethically defensible treatment goal (111). Another expressed concern has been that this type of treatment might cause a child to feel shame or other negative and maladaptive feelings (108).

Watchful Waiting

The second approach takes an intermediate therapeutic position. On the one hand, it does not recommend an early gender social transition on the grounds that the extant follow-up studies have shown that the majority of children with gender dysphoria desist for one reason or another. On the other hand, it does not explicitly recommend any type of limit-setting on the child's gender-variant behavior, with the exception that in certain environments it might be risky or dangerous to display such behavior, which Hill et al. (114) described as the "only at home" rule.

This approach also does not privilege one type of long-term outcome over another, noting that it is difficult to predict outcome for an individual child and that the more important focus should be on the child's general psychosocial adjustment and well-being. This approach does, however, include recommendations to parents that they try to encourage in their child a variety of gender-related interests and social

affiliation with children of both genders. In some respects, the “watchful waiting” label is a bit of a misnomer because clinical protocols appear to include information provided to the parents that is more than “wait-and-see.” As noted by de Vries and Cohen-Kettenis (115), appropriate limit-setting with good explanation of why the limits are set to their child may be helpful so that the child will learn “that not all desires will be met,” which is important because “someone’s deepest desire or fantasy to have been born in the body of the other gender will never be completely fulfilled.” Although social transition according to this approach is not recommended at a very young age, an increasing number of children have already socially transitioned when they come to gender identity clinics (115). Some of these children may have no clear memories of a time that they were socially living in the birth-assigned gender and have stopped talking about being born different from their experienced gender. In these cases, it is encouraged that parents create an open situation where the child has the possibility of returning to the birth-assigned gender. It is discussed with the child that when gender identity feelings change, it is nothing to be ashamed of, that nobody will be angry, that the child may speak out, and that it is good to have tried. A form of psychotherapy that helps the child to verbalize his or her feelings may be advised so that, by the time the child may come back for GnRHa, the child is able to talk about his or her feelings and can give informed consent.

Affirmative Approach

The affirmative approach theorizes that clinician and parental attempts to push children with gender incongruence toward conforming to their gender assigned at birth might produce shame and stigma that can ultimately lead to internalizing psychopathology (108). The approach considers all outcomes of gender identity to be equally desirable and affirms any gender identity the child expresses.

Though similar to the watchful waiting approach, an important departure is in its approach regarding early social transition. In the affirmative model, prepubertal children who ultimately express a desire to socially transition and live full time in their experienced gender (i.e., using cross-gender pronouns, a cross-gender name, cross-gender clothing, etc.) are allowed to do so. The approach to social transition must be carefully individualized with a nuanced understanding of the child’s gender identification and the level of support within the child’s community; there must also be an open discussion with the child highlighting that despite the social transition that the patient is free to transition back at any time (115).

Some have noted cases where this transition back to living as one’s birth gender can be particularly difficult mostly due to fear of peer judgment (116), though this must be weighed against the potential negative consequences of refusing to affirm a child’s identity and desire to transition socially. The affirmative model predicts that this lack of affirmation might lead to shame and consequent internalizing

psychopathology (117). The therapeutic relationship in these cases could also be negatively affected if the clinician strongly discourages an early transition for a patient who ultimately persists in cross-gender identification.

Critics of social transitions in prepubertal children have raised the question of whether early social transition increases the rates of gender incongruence persistence from childhood into adolescence. Indeed, a multivariate regression analysis revealed that early social transition was associated with persistence (73). However, the direction of this association cannot be determined by this study. While some believe that prepubertal social transition makes children more likely to persist, the alternative interpretation is that those likely to persist are also more likely to undergo early social transition, due to currently unidentified factors. This additionally raises the ethical question of whether persistence should be considered an undesirable outcome. The affirmative model suggests that all outcomes of gender identity are equally desirable.

Separate from the question of persistence is the question of mental health outcomes following social transition. There is a relative paucity of literature studying the effect of prepubertal social transition. One study examined 73 American prepubertal children who were transgender in a binary fashion and allowed to socially transition. Parents of these children completed short forms for anxiety and depression at an unspecified time following the transition (118). Data from these scales revealed that these children had notably lower rates of internalizing psychopathology than previously reported children who did not transition. Furthermore, socially transitioned children in this study showed developmentally normal levels of depression and only minimally elevated (subclinical) levels of anxiety. It is important to note that families in this study had a relatively high median income, raising the question of whether this cohort is representative of a broader sociodemographic cohort (119). Though this early work suggests that socially transitioned children have better mental health metrics than previously reported children who did not socially transition, future research is needed to fully understand the dynamic and long-term effects of social transition in a broader population (119).

Treatment of Adolescents

Once children have reached puberty, transgender identity persists in the vast majority of cases, and medical intervention is often considered. At present, the effectiveness of an approach that includes puberty suppression and is followed by cross-hormones and surgeries has been evaluated in two studies on the same cohort of Dutch adolescents. The first study evaluated gender dysphoria and psychological functioning at two time points; first, when the 70 adolescents entered the clinic (mean age, 13.65 years), and second, just before they started cross-hormones (mean age, 16.64 years). Of interest, while adolescents improved with regard to psychological

functioning on several domains, gender dysphoria did not improve and all adolescents went on with the next step of gender-affirming hormones (120). The second study added a third assessment, around one year after gender affirmative surgeries, when the first 55 adolescents who had been in this treatment protocol had reached young adulthood (mean age, 20.70 years). This time, gender dysphoria was resolved and psychological functioning measures had even further improved with scores that were comparable to normative samples. The same accounted for quality of life, subjective happiness, and satisfaction with life scores (121). These positive results are promising and give trust that starting treatment at a relatively young age is possible. However, the results come from only one clinic and concern a highly selected sample that received support from their parents and often their further school and social environment that started the treatment only after extensive assessment and received further mental health counseling during the years of treatment. Whether the same positive results can be expected for the larger number of adolescents that are treated at clinics that strongly vary in their approach to gender-variant adolescents has yet to be determined.

Assessing Eligibility

According to Endocrine Society Guidelines, hormonally based medical intervention may be initiated at the earliest signs of puberty (i.e., Tanner 2 or 3) (26). Other eligibility criteria include meeting criteria for gender dysphoria (termed gender identity disorder in the 2009 guidelines), experiencing dysphoria toward early pubertal changes, having adequate psychological and social support for treatment, understanding the risks and benefits of treatment, and not suffering from a psychiatric comorbidity that would interfere with treatment (26). To assess eligibility, most clinics offer an assessment by a mental health professional that sees the adolescent and his or her family over a longer period of time before decisions regarding medical interventions are made. This time is used to prepare for the long period of medical treatment with lifelong consequences that is likely to follow and weigh the pros and cons of treatment so that an informed decision can be made. Although many adolescents come with a clear wish for medical treatment, some are not sure yet and want to explore their gender dysphoric feelings more broadly. Sometimes co-occurring psychiatric difficulties like ASD with rigid thinking, severe depression with acute suicidality or anxiety with worrisome avoidance and school refusal, complicate this diagnostic work and make coming to regular medical checkups and taking medication impossible. Treatment of these psychiatric disorders may then be necessary before endocrine intervention. The importance of parental support for the psychological well-being of adolescents is widely acknowledged (122). The time that is used for assessment may also be helpful in addressing parents' concerns and improving the adolescent-parent relationship. The time that is needed before medical intervention is provided may vary for each individual case, but tends to be longer

when psychosocial comorbidities occur (115,123).

Fully Reversible Interventions (Pubertal Blockade)

The first such intervention (implemented at Tanner 2 or 3 of puberty) is pubertal blockade with GnRHa. Gonadotropin-releasing hormone is produced by neurons in hypothalamus. In prepubertal children, this hormone is secreted at very low levels. At the initiation of puberty, release of gonadotropin-releasing hormone becomes cyclical. This cyclical release of hormone results in release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. These hormones then enter the peripheral circulation, where they initiate the production of sex hormones (estrogen in natal women and testosterone in natal men). These hormones then initiate the irreversible development of secondary sex characteristics.

GnRHa (either implants, depot injections, or regular injections) maintain high levels of gonadotropin-releasing hormone in the circulation. Without physiologic cyclical fluctuations in GnRH levels, FSH and LH are not released and all downstream signaling is prevented. This allows the patient to remain in a prepubertal state (124).

Pubertal blockade prevents the development of irreversible secondary sex characteristics (voice deepening, breast development, etc.) and provides additional time for gender dysphoric children to decide if they wish to fully transition physically into the body of the opposite sex. Therefore, it does not need to be considered actual gender affirmative medical treatment, but rather may function as an extended diagnostic phase. If the GnRHa implant is removed or the injections discontinued, the effects of the medication are reversible. With removal or discontinuation of the GnRHa, the patient will undergo natal puberty. Follow-up studies into young adulthood on the first cohort of puberty-suppressed adolescents are reassuring with regard to side effects. Although there was some deprived bone density, there were no concerns regarding liver and kidney functioning and lipid profile (125,126). Some advise clinicians to evaluate bone age for these patients every 3 months (26) and have regular blood monitoring to ensure that the central axis of puberty is sufficiently suppressed (26).

Partially Reversible Interventions (Cross-sex Hormonal Therapy)

Around the age of 16, patients may choose to move onto the next intervention of cross-sex hormonal therapy with estrogen or testosterone, according to Endocrine Society guidelines. Some groups have noted that cross-sex hormones can be instituted earlier, as delaying puberty outside the developmentally appropriate age may cause social problems for these youth (127). Additional criteria for cross-sex hormonal therapy are identical to those for GnRHa in the Endocrine Society guidelines.

Cross-sex hormones will initiate the development of secondary sex characteristics

of the desired puberty. These interventions are mostly irreversible and carry a more significant side-effect profile. The most prominent side effect of estrogen therapy is hypercoagulability, though clinicians prescribing these medications should be aware of the full spectrum of side effects. Of note, this hypercoagulability can be particularly problematic for patients undergoing high-risk surgery such as vaginoplasty. Patients on these medications should be regularly monitored for serum hormone concentrations and maintained within normal testosterone and estrogen serum concentrations for their desired gender. Spironolactone has been used for its antiandrogenic properties in select cases but is generally not considered a first-line treatment given its unfavorable side-effect profile as a diuretic (26).

Irreversible Interventions (Gender-Affirming Surgeries)

At the legal age of adulthood, patients may choose to undergo a variety of surgical interventions, including vaginoplasty, phalloplasty, scrotoplasty, breast augmentation, facial reconstruction, hysterectomy, reduction thyroid chondroplasty, among others. Patients should be carefully counseled on the risks and benefits of surgery. Specific surgical interventions are many and are out of scope for the purpose of this review. Of note, some surgical interventions may be considered earlier in the course of treatment. In the WPATH's Standards of Care, mastectomies are being considered earlier than age 18 (27).

Fertility Considerations

There is a paucity of research on the effects of pubertal blockade and cross-sex hormonal therapy on future fertility. Interested patients should be counseled on fertility preservation options early in treatment. Include LGBT Health study showing that most transgender youth do not desire fertility preservation, however most adults which they had. More longitudinal research needed (128).

SUMMARY

Gender incongruent and gender dysphoric youth represent a vulnerable demographic with high rates of co-occurring psychiatric conditions and suicidal behavior, likely secondary to minority stress and dysphoria related to living in a body that does not match one's experienced gender. Prepubescent children with gender-variant behavior or identification are best supported with psychotherapy. For those children who continue to have strong cross-sex identification in adolescence, pubertal blockade, and cross-sex hormone therapy to align patients' bodies with their identities have been shown to improve mental health outcomes.

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